



Royal College of
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Developing New Pharmaceutical Treatments for Obstetric Conditions

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1. Introduction

Maternal and perinatal disease causes about 7% of the global burden of disease,¹ with only modest progress being made towards achievement of the Millennium Development Goals. One aim of global health research and development (R&D) is to produce new drugs for neglected diseases, but R&D investment in maternal and perinatal health remains small and nonstrategic. Only a few drugs, such as mifepristone in the context of pregnancy termination and aspirin and prostaglandins, for example, have been shown to be effective in pregnancy. There is currently a 'drought' of new drug development² and a review of an industry database found that in 2007 there were 1636 drugs under development for neurological indications, but only 17 for maternal health indications.² Obstetrics had only 1-5% of the drug pipeline of other mainstream specialties and fewer drugs in development than for some single diseases such as Crohn's disease or amyotrophic lateral sclerosis.³

This paper discusses the challenges in developing therapeutics in obstetrics and identifying best practice.

2. Historical perspective

Teratogenicity is one of the main concerns with drug development in obstetrics.⁴ The teratogenicity associated with the use of thalidomide for prevention of hyperemesis⁵ led to changes in drug development and licensing processes, and the requirement for better evidence standards.⁶ Pharmaceutical regulations were strengthened to protect patients' interests and to assess information presented by the manufacturers on new drugs in an unbiased way. The increased risks of clear cell adenocarcinoma of the vagina and cervix, and of breast cancer found in the daughters of women who took diethylstilboestrol for the prevention of early miscarriage changed medical thinking about the embryological development of the genital tract and the mechanism of carcinogenesis.⁷ In utero exposure can lead to alterations in organ development and malignant transformation that may only manifest decades later and might even have third generation effects. Long-term follow-up is vital to ensure that all types of teratogenesis are captured.

3. A balance of risks

Medication during pregnancy is increasingly common, with over 80% of pregnant women having at least one prescribed drug⁸ either as a continuation of pre-existing therapy or as treatment for pregnancy-associated problems. Women may also access healthcare information from sources other than their physicians, such as internet sites, which may provide incorrect information.⁹ Very few drugs are licensed for use in pregnancy. For many women the potential harm of taking a drug that may cause teratogenesis needs to be weighed against the risk to their health, or that of the unborn child, of not taking the medication. This is a common predicament. One example is anti-epileptic drugs that are associated with an increased risk of neural tube defects, cardiac abnormalities and neurodevelopmental deficits.¹⁰ Ceasing to take anti-epileptic drugs during pregnancy can lead to tonic-clonic seizures, with significant adverse health outcomes for the woman or the fetus, including disability or even death.^{11,12}

4. The pharmaceutical industry and obstetric drug development

Threatened preterm labour, fetal growth restriction (FGR) and pre-eclampsia are excellent examples where effective agents could make a major difference to long-term health and provide associated financial benefits for the pharmaceutical industry. There are many reasons why such companies may choose not to develop drugs for use in pregnancy. The market is relatively small and the duration of drug administration is brief compared to long-term conditions where drug administration often spans many

years in a relatively large proportion of the population. The multifactorial cause of obstetric conditions means that it is unlikely that all patients can be treated effectively with a single drug, making study design and analysis more complex and requiring a relatively large number of subjects and high costs. In addition, the lack of an accurate diagnostic test for many obstetric conditions often makes identification of appropriate subjects difficult. Pregnancy-specific maternal changes may influence drug metabolism and there are concerns about adverse effects on the fetus leading to financial liability. For example, in preterm labour, a delay in delivery of the baby could increase the fetal exposure to an adverse intrauterine environment (such as infection). For this reason, trials have to demonstrate effective tocolysis as well as improved neonatal and infant health, requiring long-term follow-up across more than one specialty and increased costs. It is therefore not surprising that, on the whole, the pharmaceutical industry has chosen not to develop and license drugs for use in pregnancy.

Repositioning or 'repurposing' existing licensed drugs has huge advantages and is widely practised in the fields of cancer and infectious diseases, generating huge profits and leading to the development of a whole repurposing industry.¹³ The repurposed drug has usually already passed a significant number of toxicity tests and has a known safety profile which reduces the costs of bringing it to market. The intellectual property position is much stronger if the innovator patent has not expired, regulatory exclusivity is obtained or if a new patent can be assigned to a repositioned drug based on a new indication which has a different formulation, dosing regimen or route of delivery that is clearly different from the parent drug. One such successful example is thalidomide, which has been shown to be safe and very effective in pain relief in leprosy and Kaposi sarcoma. In paediatrics, databases of drugs with licences for use in children have been generated to provide a starting point for repurposing drugs.¹⁴ No such databases exist for use in pregnancy.

5. Use of unlicensed drugs in pregnancy

A licensed drug has satisfied the regulatory authorities that it has undergone a rigorous evaluation of efficacy and safety. The decision about whether to apply for a licence for a drug remains with the manufacturer. This is commonly governed by commercial reasons, given the large cost of obtaining a licence. Indeed, a patent holder may decide not to apply for a drug indication if it requires reproductive toxicology and maternal and fetal investigations because of insufficient economic interest, even when the drug could be of huge patient benefit. This conflict was highlighted with misoprostol, a prostaglandin E1 analogue that was licensed for the prevention and treatment of gastroduodenal ulcers and has been on the market since 1985.¹⁵ Despite abundant literature demonstrating its safety and efficacy, the manufacturer and patent holder did not apply for licences for reproductive health indications, denying women access to a cheap and stable prostaglandin, of especial value in the developing world. The drug is now on the World Health Organization Model List of Essential Medicines for prevention of postpartum haemorrhage and has approval in many countries for gynaecological indications as part of the regimen for the termination of pregnancies.

Clinicians sometimes choose an unlicensed product for use in pregnancy even when a licensed alternative is available. Tocolysis with unlicensed drugs such as nifedipine, for example, is not uncommon within the National Health Service, largely because it is cheap. Yet atosiban, an oxytocin receptor antagonist, which is licensed in Europe for the treatment of uncomplicated spontaneous threatened preterm labour and has undergone evaluation in pregnancy including placebo-controlled trials, is less commonly used, most likely because of the relatively higher cost.^{16,17} One solution to this issue could be to reduce the costs associated with meeting the licensing requirements.

6. Teratogenicity during embryological and fetal development

The decision on whether an environmental exposure is a teratogen is based in part on the criteria described by Hill¹⁸ that consider the strength and consistency of the association, its specificity, temporal

relationship, coherence, biological gradient and plausibility.¹⁹ Many human teratogenic exposures have been identified by 'astute clinicians', usually from observing cases of distinctive malformations associated with unusual exposures.²⁰ Specific drugs can be associated with particular malformations due to the disruption of embryonic or fetal development at a certain time. For example, isotretinoin malformations are due at least in part to the inhibition of migration of cranial neural crest cells during early embryonic development, leading to abnormalities of the cranium/face, heart, thymus and central nervous system if the embryo is exposed at less than 28 days of gestation. These types of malformation were predicted by animal studies. The likelihood of an effect in humans may be difficult to predict since it is determined by the drug half-life in vivo, placental transfer, maternal metabolism of the drug into a potentially more toxic metabolite, and the sensitivity of the human embryo, all of which are different to animals.¹⁹ Even after licensing it may therefore not be possible to characterise the potential of a drug for teratogenicity sufficiently when it first enters clinical practice, such that postmarketing surveillance is particularly important when drugs are first used in pregnancy.

7. Reproductive toxicology

7.1 *Human versus animal pregnancy*

Testing new medicinal products for reproductive toxicity aims to identify possible hazards to human reproduction. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines govern reproductive toxicity studies in women and men,²¹ specifying that any programme should allow exposure of the novel chemical to all stages of development throughout one complete life cycle: for example, from conception in one generation through to conception in the following generation. Where more than one investigation is used there must be an overlap between studies so that no gaps are left between key stages. This is especially relevant if a drug affects fertility, when there may not be adequate numbers of pregnant animals or fetuses to assess developmental toxicity properly in utero. In practice, a number of overlapping studies are conducted to cover fertility and early embryonic development, embryo-fetal development, and pre- and postnatal development, including lactation and weaning.²² All studies need to be conducted under Good Laboratory Practice (GLP) conditions, which are extremely costly.

It is not surprising that teratogenic effects of drugs seen in humans are not necessarily observed in preclinical reproductive toxicology studies in animals. Placental, embryological and fetal development in the human is unique in many ways. For example, the deep trophoblast invasion of the spiral arteries does not occur to the same extent, if at all, in other mammals. The human placenta is monochorial with a single layer of cells between the maternal and fetal blood in the third trimester. In contrast, the rodent placenta is trichorial (three layered), while in ruminants the barrier is six layers thick, preventing the passage of some proteins, such as immunoglobulins. Spontaneous multiple pregnancy is unusual in women but is common for most other laboratory and experimental mammals.

The last half of human pregnancy is particularly important for the development of the fetal brain and lungs, but in small animals, such as rodents and rabbits, gestational length is considerably shorter (21-23 and 30 days respectively) than in women and much of the development that takes place during fetal life in the human occurs in the neonatal period in these animals.

7.2 *Neonatal considerations*

A concern for the breastfeeding mother can be the risk of transfer of drugs into her milk, with the potential for adverse events. In the breastfeeding mother, the measurement of medications produced in breast milk is not technically challenging, but it is important to ensure that assays are performed as part of the anticipated drug development. Data on the risks of breastfeeding in patient information leaflets are often not available when, as is common, the drug has not been fully evaluated for safety in pregnancy or breastfeeding. A general default position is often to assume that either insignificant amounts of the

drug are transmitted or, when the drug has to be continued, that the mother should not breastfeed. In some cases when there is no information available, women may stop medication, with the potential to cause harm to the mother, or a risk for the infant if breastfeeding is safer than formula feeding. Despite these concerns, a comprehensive review of the published cases on infant adverse reactions from drugs in breast milk suggested that the risks were low²³ and a recent statement from the American Academy of Pediatrics endorsed this.²⁴

8. Establishing the effectiveness of drugs for obstetric conditions

8.1 *Animal models of obstetric conditions and their problems*

Vascular responses to agents for potential use in pre-eclampsia or FGR can be evaluated in blood vessels collected from the myometrium or omentum of pregnant women who undergo delivery by caesarean section. The effect of a drug on human trophoblast growth, development and function, or placental transport can be tested in villous explants where the syncytiotrophoblast regenerates after 24 hours and provides an intact surface to which drugs may be applied. Perfusion of the whole human placenta allows drugs to be applied to the maternal side and their movement across the placental barrier monitored; as well as their short-term effect (less than 9 hours) on barrier integrity, placental function can be evaluated. Alternatives to animal testing include using the human embryonic stem cell test²⁵ and human endometrial explants, both of which have been studied in the European Union (EU)-funded ReProTect consortium.²⁶ There is little information on in vitro attempts to study the effect of drugs on human fetal tissues.

Ultimately, animals are needed to study the therapeutic effect of drugs in vivo. There are a number of natural, genetic and adapted animal models of obstetric conditions; however, in many cases there are problems in extrapolating such findings to human obstetric conditions. Transgenic mouse models are increasingly available that can model certain aspects of obstetric disease. Care must be taken to choose an animal model that is appropriate to the question being addressed, bearing in mind differences in placentation, gestation, parturition, stage of development at birth, the immune system and the number of fetuses.²⁷

For FGR, there are some natural 'runt' of the litter animal models available.²⁷ More commonly, FGR can be created by reducing the uteroplacental blood supply by ligating the uterine arteries, by maternal nutrient restriction or by reducing the volume of the functioning placenta. There are transgenic mouse models of FGR where, for example, expression of insulin growth factor or endothelial nitric oxide synthase has been manipulated. Many of these interventions are extreme and do not resemble the human FGR condition where the maternal nutrient intake is usually normal and the uterine circulation maintained. Although many of these models have a higher stillbirth rate and could be considered for this research area, a model for stillbirth within the normal ranges of fetal weight is not available.

Pre-eclampsia seems to be restricted to humans and no natural animal models exist. Reduced uterine perfusion pressure models in the rat and nonhuman primate closely mimic the hypertension, immune system abnormalities, systemic and renal vasoconstriction, and oxidative stress in the mother, as well as FGR in the offspring, but they do not have the abnormal placentation that ultimately leads to placental ischaemia in humans. Transgenic models based around abnormalities in *HIF1 α* , or overexpression of soluble Flt-1²⁸ or STOX1, a transcription factor involved in trophoblast proliferation and invasion, are now providing a platform for initial testing of drugs that may be able to improve the maternal phenotype.

Developing therapeutics to prevent or treat spontaneous preterm labour has been hampered by the lack of an appropriate animal model. There are major differences in the mechanisms of labour in women compared to most other animals; for example, there is a fall in plasma progesterone prior to the onset of labour in most mammals but not humans. Furthermore, spontaneous preterm labour is multifactorial,

whereas many animal models involve administration of a single drug or compound to initiate preterm labour. For the reasons described above, the key outcome should usually be an improvement in neonatal outcome rather than an effect on pregnancy duration. Such outcomes can rarely be determined in animal models that induce preterm labour artificially, not least because the technique used to initiate labour may have fetal or neonatal implications.

8.2 *Clinical trials during pregnancy*

The regulations governing the inclusion of potentially childbearing women into clinical trials has considerable regional variation and experts in regulatory affairs are usually required to recommend the best course of action to comply. Traditionally, to introduce a drug into clinical practice, it passes through four phases: phase I trials to evaluate safety, determine a safe dosage range and identify side effects in a small group of people (20–80); phase II trials (100–300 people) to evaluate safety and to begin to determine efficacy; phase III (1000–3000 or more people if the chosen primary outcome measure has a low frequency e.g. neonatal death) where it is compared to existing treatments; and phase IV postmarketing studies to delineate additional information, such as the treatment risks, benefits and optimal use. The lack of effective clinical diagnoses algorithms, combined with the multifactorial nature of obstetric conditions, makes the design of simple clinical trials challenging.

Teratology Information Services (TIS) play a key role in screening for potential new human teratogens, particularly in gathering information about newly marketed medications.²⁹ There are now two large TIS networks: the Organization of Teratology Information Specialists that serves the USA, Canada and Asia, and the European Network of Teratology Information Services. These organisations bring together multidisciplinary expertise across genetics, obstetrics and therapeutics to address questions regarding the potential of specific agents to interfere with normal embryonic or fetal development, conducting prospective cohort studies in women who are pregnant and have had an exposure of interest and comparing them with an unexposed comparison group.

9. Ethical and regulatory considerations

There are complex ethical issues associated with obstetric clinical trials. Ethical committees may be reticent about approving trials in pregnancy as they are uncommon and there is the potential for adverse fetal effects. Without adequate testing, however, we will be unable to evaluate drugs properly, raising different but serious ethical concerns.

Clinical governance advice³⁰ concludes that it is reasonable to take consent in labour as long as appropriate time is available for discussion and consideration. The recommended time to approach women and the level of information provided depend on how frequent the occurrence is. Given that any treatment administered to the mother will often need to demonstrate a beneficial effect on the neonate, with commensurate long-term follow-up required, trials are further complicated, with an additional knock-on effect for recruitment.

A further difficulty which can prevent commercial drug development is the apparent conflict between the requirements of the ethical and regulatory authorities. For example, there are no therapeutic trials demonstrating long-term benefits of delaying delivery in preterm labour, such that RCOG guidelines state that it is reasonable not to use tocolytics.³¹ It is therefore logical to assume that there is equipoise regarding the administration of tocolysis. However, ethical committees (particularly in the USA) are unwilling to allow placebo-controlled trials because tocolysis is seen to be the standard of care. Even where an investigative drug is administered, approval of study protocols may require rescue tocolysis (or even a second-line tocolytic), thereby preventing accurate evaluation of maternal, fetal and neonatal outcomes. Despite this, regulatory approval may require demonstrable improvements in outcome compared with placebo.

The decision by regulatory authorities on whether to license a drug comprises two different but complementary assessments. Firstly, there is an assessment of the quality and adequacy of data presented by the drug developers, which is commonly based on studies of efficacy in animal models and safety reproductive toxicology studies as described above. Secondly, there is consideration of whether the expected benefits outweigh the harms, which requires a value judgement of the risks and benefits of the treatment.

Increasingly it is recognised that patients are an important part of this process and that there is a need to combine respect for patients' value judgements with scientific rigour. Research partnerships have been launched to improve drug development and regulation. The Critical Path Institute in the USA³² encourages pharmaceutical companies to share their placebo/control data from clinical trials and works with patient organisations to target specific diseases. Similarly the Innovative Medicines Initiative in the EU³³ has over 40 projects and a €2 billion budget aiming to improve the drug development process by supporting more efficient discovery and the development of better and safer medicines. Current projects are mainly on chronic diseases, cancer and neurological disease; obstetric conditions are yet to feature.

10. The pharmaceutical industry

For pharmaceutical companies, two scenarios of obstetric drug development need to be considered: firstly, a decision to target obstetric conditions as a strategic focus for investment in discovery and development; and secondly, a recognition that medicines developed for other acute or chronic disorders may be used in pregnancy, for which specific dosimetry and risk-benefit recommendations are likely to apply.

Industry-sponsored clinical trials prior to registration or even post marketing rarely prioritise use of a drug in pregnancy. This can lead to widespread off-label drug use about which there is often limited information in datasheets. Collaborative efforts between academia and industry could play an important role in backfilling some of the key gaps in evidence to support appropriate use of commonly used medicines in pregnancy, but currently a large observational experience of a treatment without significant resulting complications makes it unlikely to attract funding support.

The high costs of drug discovery and development have been widely reported³⁴ and pharmaceutical companies are increasingly concentrating their efforts on areas with a higher potential return on investment. There is a move away from the traditional blockbuster model towards more diverse therapeutic areas, including rare diseases, in which shorter development times and opportunities for accelerated approval can offset smaller market revenues. Unfortunately, obstetric indications not only fall short in attractive sales forecasts, but the perception of long and difficult clinical trials, onerous regulatory hurdles and the potential risk of litigation mean that this therapeutic area is not prioritised by many companies. Securing orphan disease designation for medicines for rare diseases is one method to reduce the costs of commercialisation of a new therapeutic. The scheme is further described in Appendix I.

As the standards of care increasingly differ across countries, it is more difficult for pharmaceutical companies to design a clinical trial programme that meets the needs of all major markets. The Food and Drug Administration (FDA) in the USA has approved only a dozen medications for use during pregnancy.³⁵ Atosiban is notable as an obstetric medicine which has received regulatory approval in Europe and several other countries worldwide. However, its rejection by the FDA is well documented, with the transcript of the advisory committee highlighting the lack of consensus on clinical trial requirements and validated endpoints for acute tocolytic treatments.³⁶

In 2011, Makena® (hydroxyprogesterone caproate; Lumara Health, Waltham, Massachusetts, USA)³⁷ received accelerated approval by the FDA for prevention of preterm delivery in high-risk women on the basis of a reduction in the proportion of preterm births at 37 weeks demonstrated in a single trial,

with a postmarketing commitment to demonstrate that this translates into neonatal benefit. For an acute intervention for preterm labour, however, the FDA requires two pivotal placebo-controlled trials from 24 to 36⁺⁶ weeks of gestational age, each demonstrating improved neonatal outcome, with a 2-year follow-up of all neonates completed prior to submission of the New Drug Application. The sheer scale and design, time and cost implications to meet these expectations make it highly unattractive for any company to pursue such a plan, unless more innovative regulatory pathways, patent incentives and/or litigation protection strategies are established.

11. Recent regulatory and multiagency initiatives

A number of recent initiatives have been set up to drive translation of new therapeutics into clinical practice and are described in detail in Appendix II. Examples include improvements in accessibility to scientific advice and protocol assistance via the Committee for Medicinal Products for Human Use at the European Medicines Agency (EMA). This allows informal dialogue at any stage of drug development ranging from drug quality, proposed reproductive toxicology studies and trials.

An important new area is the development of clinical trials networks globally, for example, the National Institute for Health Research Office for Clinical Research Infrastructure and the Obstetric Clinical Research Networks in the UK and the Global Obstetrics Network,³⁸ that are working to coordinate obstetric research. In the USA, the 'Treating for Two' initiative (Appendix II) is concentrating only on therapeutics for acute or chronic maternal conditions that occur just before or during pregnancy. Nevertheless, the initiative is important and the processes developed may be adaptable to evaluation of therapeutics for obstetric conditions.

In paediatrics there has been significant progress where the initiation of a paediatric investigational plan (PIP) is revolutionising the testing of medicines on children internationally. PIPs aim to ensure that the necessary data to support the authorisation of a medicine for children are obtained through studies in children, when it is safe to do so. They include a description of the measures to adapt the medicine's formulation to make its use more acceptable in children of all age groups, from birth to adolescence. The Paediatric Regulation that came into force in the EU on 26 January 2007 is driving this change. No such system yet exists for pregnant patients.

12. Opinion

The consequences of obstetric diseases have a huge effect on the quality of life of individuals and their carers and are a drain on the world's financial resources because they can have lifelong effects requiring extensive educational, social and health input. The development of new drugs for use in obstetrics will require both clinical and commercial inertia to be overcome. The barriers to drug development include worries about teratogenicity, a lack of suitable animal models, high development costs, difficulty in trial design and the challenges posed by regulatory and ethical issues.

We suggest a number of strategies to improve the development of new obstetric therapeutics:

1. The formulation of ways to stimulate repurposing of drugs specifically for obstetric indications is urgently needed, with associated funding to develop animal models of obstetric disease in which to test out potential therapeutic agents.
2. Support for research into the development of new 'models' to explore teratogenesis and placental transfer in human tissues including the placenta, samples from fetal terminations and breast milk, all with the appropriate patient and ethical approval. This will require an acceptance of research into the use of termination of pregnancy samples for testing out new therapeutics from patients, the public and the regulators.

3. Further development and use of diagnostic methods to detect obstetric disease early to enable clinicians and the pharmaceutical industry to design high quality, focused clinical trials.
4. The coming together of the academic community, regulators, pharmaceutical industry and the government to stimulate obstetric therapeutic research by, for example, exploring ways to expand and concentrate innovative regulatory pathways and litigation protection strategies (e.g. government take responsibility for indemnity) in the specific area of obstetric therapeutics.
5. The establishment of formal funded registries with good linkage to paediatric developmental outcome data in order to dramatically improve information on the safety of drug exposures during pregnancy. The obligatory reporting of off-licence uses of drugs in pregnancy would mean that data were accumulated for large numbers of exposures very quickly, without having to rely on ad hoc reporting by interested clinicians, often using retrospective data and postmarketing surveillance data from industry.
6. The establishment of ways to improve the provision of medicines for obstetrics following the progress made in paediatrics; for example, an 'obstetric investigational plan' could be proposed and considered at a legislative level to increase the testing of medicines on women who are pregnant. Secondly, a 'repurposing' database of drugs with licences for use in obstetrics could be useful.
7. Curtailment of the use of unlicensed drugs for obstetric conditions, when licensed drug alternatives are available, in order to encourage pharmaceutical companies to spend the time and money investigating and licensing drugs in pregnancy.
8. Full acceptance of the voices of patients, which are increasingly being heard via patient-public partnerships such as the James Lind Alliance and are now driving the research agenda for the benefit of patients. Developing drugs in obstetrics is not without risk, but the value judgements of patients about their needs and the risk of a treatment should be explored further, to balance the regulatory hazards that are identified.

All healthcare professionals who care for pregnant women should be involved in the common aim of developing new treatments, ensuring that patients have the opportunity to take part in clinical trials and to witness the implementation of research findings into clinical practice. NHS England's *Research and Development Strategy* states that 'Research is everybody's business'. This includes pregnant women and their babies.

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Appendix I: Orphan disease designation

Both the EMA (EMA Committee for Orphan Medicinal Products) and the FDA (FDA Office of Orphan Products Development) offer incentives for sponsors developing orphan medicines. These include protocol assistance and 10-year market exclusivity (EMA) and tax credits for qualified clinical testing (FDA); there are also orphan product grants available for clinical studies on safety and/or effectiveness (FDA).

The criteria for orphan approval are:

1. The therapeutic must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating (as many obstetric diseases are).
2. The prevalence of the condition must be low (less than 5 in 10 000 for EMA, fewer than 200 000 people in the USA) or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development.
3. No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

To date there has been one successful orphan designation application to the EMA for a new therapeutic in pre-eclampsia (S-nitrosoglutathione) and four to the FDA (three existing drugs, misoprostol, progesterone and hydralazine, and one new drug for prevention of congenital cytomegalovirus transmission to the fetus).

Appendix II: Recent regulatory and multiagency initiatives

Initiative	Resource	Aim
Medicines and Healthcare Products Regulatory Agency (MHRA): Early Access to Medicines Scheme	Provides an early scientific opinion on the benefit/risk balance of medicines for patients with life-threatening or seriously debilitating conditions, based on the data available at the time of the submission.	To stimulate investment in and speed up access to drugs that do not yet have a marketing authorisation when there is a clear unmet medical need.
National Institutes of Health: LactMed® ³⁹	A searchable database of the latest peer-reviewed research on medications and breastfeeding, updated monthly.	To provide information on drugs and other chemicals to which breastfeeding mothers may be exposed, the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant. Suggested therapeutic alternatives to those drugs are provided.
National Center on Birth Defects and Developmental Disabilities of the Centers for Disease Control and Prevention: Treating for Two: Safer Medication Use in Pregnancy. ⁴⁰	Agreed priority setting for maternal conditions in pregnancy, a systematic review process to assess the maternal and fetal effects of exposure to medications used to treat the condition, and a method to develop treatment recommendations for the conditions reviewed. ⁴¹	To identify the best alternatives for treatment of common conditions during pregnancy and during the childbearing years.

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